

Review Article

A Review of the Evaluation and Management of Peripheral Vascular Disease

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ABSTRACT

Peripheral vascular disease (PVD) is a prevalent and leading public health problem. It is defined as partial or complete occlusion of one or more arteries, usually of the pelvis or lower limbs, caused by atherosclerosis. This condition is manifested by symptoms of compromised blood flow with exercise or, in severe cases, at rest. Patients with compromised blood flow to the extremities most commonly present with pain (claudication) of a muscle group. PVD is associated with increased

cardiovascular mortality and morbidity. Unfortunately, it is often under-diagnosed and under-treated. Ankle-brachial index (ABI) is an inexpensive and reliable test for the screening of peripheral arterial disease. Aggressive control of risk factors, exercise rehabilitation and pharmacological interventions are highly effective in improving the symptoms of intermittent claudication and in reducing cardiovascular events.

KEYWORDS: ankle brachial index (ABI), atherosclerosis, exercise, intermittent claudication, risk factors

INTRODUCTION

This report will offer a review of the evaluation and management of peripheral vascular disease (PVD). PVD is generally defined as partial or complete occlusion of one or more arteries, usually of the pelvis or lower limbs, caused by atherosclerosis. This condition can be asymptomatic, or manifest by symptoms of compromised blood flow with exercise or, in severe cases, even at rest. Patients with compromised blood flow to the extremities most commonly present with pain of a muscle group. Intermittent claudication (derived from the Latin word for limp) is defined as a reproducible discomfort of a defined group of muscles that is induced by exercise and relieved with rest. This disorder results from an imbalance between supply and demand of blood flow that fails to satisfy ongoing metabolic requirements.

EPIDEMIOLOGY

Data from the Framingham study^[1] found that onset of symptomatic disease, defined by intermittent claudication, increased ten times in men from age 30-34 to 65-74 years (with an incidence of 6/10,000 and 61/10,000 respectively). On the other hand, in women, onset increased

almost twenty times from the younger to older age groups (3/10,000 and 54/10,000 respectively)^[1]. Estimates of prevalence are also strongly dependent on the age of the examined population. Within population, prevalence rates rise markedly with increasing age^[2,3]. Reported intermittent claudication prevalence has varied. Studies have reported prevalence between 3.8 to 33% on measurements by ankle-brachial index^[4-6]. Prevalence rates also change when more liberal criteria for symptomatic disease are employed. It is very important not to underestimate the importance of peripheral vascular disease. Studies also demonstrated that populations with PVD have markedly increased prevalence of coronary arteries disease and cerebrovascular disease^[7].

ETIOLOGY

Although numerous diseases can cause intermittent claudication, the vast majority of patients with claudication suffer from peripheral atherosclerosis. The clinical history can help differentiate among some of the less common causes of this disorder. History of limb trauma, radiation exposure, vasculitis or ergot use represents some important clues to the etiology of claudication^[7]. Non-arterial pathologic conditions

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should also be considered in the differential diagnosis of limb discomfort. These include: deep venous thrombosis, musculoskeletal disorders, peripheral neuropathy, and spinal stenosis (pseudoclaudication)^[7].

RISK FACTORS

Intermittent claudication is largely a disorder of the elderly. It is estimated that at least 10% of persons over the age of 70 years have claudication. Claudication is growing as a clinical problem due to the increasingly aged population in developed countries. The clinical characteristics that favour the development of peripheral vascular atherosclerosis are similar to those that facilitate the development of coronary atherosclerosis. These include: diabetes mellitus, hyperlipidemia, cigarette smoking, and hypertension^[8]. Framingham Heart Study demonstrated that the odds ratio for developing intermittent claudication was 2.6 for diabetes mellitus, 1.2 for each 1 mmol/L elevation in the serum cholesterol concentration, 1.4 for each 10 cigarettes smoked per day and 1.5 for mild and 2.2 for moderate hypertension^[8]. In addition, diabetic patients have worse arterial disease and poorer outcome than non-diabetics^[9]. In addition, several emerging new risk factors have been described. One of them is hyperhomocysteinemia. Homocysteine is a sulphur-containing amino acid integral to the methionine metabolic pathway. Its elevated levels are associated with PVD^[10].

CLINICAL PRESENTATION

Patients with PVD often present with typical symptoms. However, many patients are asymptomatic. Perception of claudication can vary from severe debilitating discomfort at rest to a bothersome pain of seemingly little consequence. The severity of symptoms depends upon the amount of stenosis, the collateral circulation, and intensity of exercise. The location of the pain depends upon the location of the vascular disease. Patients may therefore present with buttock, thigh, calf or foot claudication, either singly or in combination. Fontaine and Rutheford are both accepted classification systems for PVD^[11]. Each scale grades PVD from asymptomatic to gangrene or major tissue loss. These classification systems can be applied when evaluating the baseline status and progression or improvement of disease symptoms. Physical examination can be normal, but commonly demonstrates diminished pulses below the level of stenosis with occasional bruits over stenotic lesions and evidence of poor wound healing over the area of decreased perfusion^[12]. Other physical findings may include a unilaterally

cool extremity, a prolonged venous filling time, shiny skin, hair loss, skin atrophy and nail changes^[12]. Different grading systems are used when describing the presence, absence and intensity of pulses. The Trans Atlantic Inter-Society Consensus (TASC) group for the management of PVD grades pulses that are absent, diminished or normal as grade 0, grade 1 or grade 2, respectively^[11]. Pulse findings should coincide with the location of pain on ambulation and should be supported by the non-invasive studies that are obtained.

A more severe form of PVD is limb threatening ischemia. This condition occurs when arterial blood flow is insufficient to meet the metabolic demands of resting muscle or tissue. It is the most common indication for lower extremity arterial reconstruction. The major manifestations of limb threatening ischemia are rest pain, ischemic ulcers, and gangrene^[11,12].

INVESTIGATIONS

In patients with suspected PVD based upon the history and physical examination, non-invasive tests are performed to confirm the clinical diagnosis and to further define the level and extent of occlusion. They include ankle-brachial index (ABI), exercise treadmill test, segmental limb pressures, segmental volume plethysmography, and ultrasonography. Invasive testing such as contrast angiography remains the gold standard in the evaluation of lower extremity ischemia. It is performed in patients without contraindication who are expected to undergo revascularisation.

Ankle-brachial index is a simple and inexpensive method to confirm the clinical suspicion of PVD. It measures the resting and post-exercise systolic blood pressures in the ankle and arm. This measurement is referred to as the ankle-brachial index or ratio and provides a measure of the severity of PVD. Calculation of the ankle-brachial index is performed by measuring the systolic blood pressure by Doppler probe in the brachial, posterior tibial, and dorsalis pedis arteries^[13,14]. The highest of the four measurements in the ankles and feet is divided by the higher of the two brachial measurements. The normal ABI is 1.0 to 1.3, since the pressure is higher in the ankle than in the arm. Values above 1.30 suggest a non-compressible calcified vessel. An ABI below 0.9 has 95% sensitivity and 100% specificity for detecting angiogram-positive PVD and is associated with > 50% stenosis in one or more major vessels^[13,14]. An ABI between 0.40 and 0.90 suggests an arterial occlusion often associated with claudication. An ABI below 0.4 represents advanced ischemia. The dynamics of blood flow across a stenotic lesion depend in part

upon whether the patient is at rest or exercising and upon the severity of occlusion. Exercise normally decreases vascular resistance and increases blood flow. A stenosis of less than 70% usually is not sufficient to decrease blood flow at rest or to produce systolic pressure gradient. Exercise in such patients induces or increases a systolic pressure gradient across the stenosis. These changes can be detected by a fall in the ABI followed by recovery. Thus, exercise testing is a sensitive method for evaluating patients in whom the resting ABI is normal^[15].

Once the presence of arterial occlusive disease has been verified using ABI at rest or exercise, the level and extent of PVD is routinely assessed by segmental limb pressures^[16]. Segmental volume plethysmography is the measurement of volume change in an organ or limb. It is usually used in conjunction with segmental limb pressures to assess the level of PVD. The technique is performed by injecting a standard volume of air into pneumatic cuffs placed at various levels along extremity. Volume changes in the limb segment below the cuff are translated into pulsatile pressures, which is detected by a transducer and then displayed as a pressure pulse contour. A change in the pulse volume contour indicates arterial obstruction^[17,18].

Ultrasonography is accurate in detecting PVD. However, resting segmental pulse volumes, and systolic pressures are the initial screening tests. Ultrasonography is currently used to assess anatomy, hemodynamics and lesion morphology^[19]. It has been suggested that the main purpose of ultrasonography is to avoid diagnostic angiography before intervention in patients with occlusion proximal to the calf^[20].

MANAGEMENT OF PERIPHERAL VASCULAR DISEASE

Therapy may involve medical, percutaneous, and/or surgical approaches. Most patients with peripheral vascular disease are treated initially with medical therapy. The medical management of moderate to severe intermittent claudication secondary to PVD involves risk factor modification, exercise training or rehabilitation and pharmacologic therapy.

RISK FACTOR MODIFICATION

The principal risk factors for the development of obstructive peripheral atherosclerosis are cigarette smoking, diabetes mellitus, hypertension and hyperlipidemia. It has been demonstrated that 69% of the occurrence of PVD is attributable to these cardiovascular risk factors^[21]. Cigarette smoking

was the most important factor. Cessation of cigarette smoking reduces the progression of disease and lowers the incidence of rest ischemia among those who quit^[22]. There are no trials which have directly evaluated the effects of antidiabetic therapy upon the natural history of PVD. However, aggressive control of blood sugar reduces the risk of microvascular complications^[23]. Hypertension is a major risk factor for PVD. There are still no data to demonstrate whether antihypertensive therapy alters the progression of claudication. Nevertheless, hypertension should be controlled to reduce morbidity from cardiovascular and cerebrovascular disease. In addition, the angiotensin converting enzyme inhibitors may provide added protection against cardiovascular events in patients with PVD^[24]. There are numerous studies which demonstrate that lipid lowering agents, especially statin therapy, have beneficial effect upon progression of PVD^[25,26].

EXERCISE REHABILITATION

Several studies have demonstrated the benefit of exercise rehabilitation programs in reducing symptoms of claudication. Exercise improves endothelial dysfunction by causing increases in nitric oxide synthase and prostacyclin, thus causing vasodilatation^[27]. Exercise also reduces the local inflammation that is induced by muscle ischemia by decreasing free radicals production^[28]. One study demonstrated that exercise may induce vascular angiogenesis^[29]. Exercise has been found to decrease red cell aggregation and increase the filterability of the blood^[30]. Patients should be referred to a claudication exercise rehabilitation program. These programs consist of series of sessions lasting 45-60 minutes per session, involving use of either motorized treadmill or a track to permit each patient to achieve symptom-limited claudication. The initial session includes 35 minutes of intermittent walking. Walking is then increased by 5 minutes each session until 50 minutes is achieved, surrounded by warm-up and cool-down sessions of 5 to 10 minutes each^[11]. Ideally, the patients attend at least three sessions per week, with a program length of more than three months. Most patients can expect improvement within two months. It has been demonstrated that supervised walking program can improve symptom free walking distance up to 123% from baseline after 12 weeks^[31].

PHARMACOLOGIC THERAPY

Pharmacologic therapy of PVD is primarily confined to symptomatic relief or slowing progression of the natural disease. Data on the use of currently available antiplatelet agents indicate

that only modest improvement in claudication symptoms can be expected^[32,34]. Aspirin (ASA) is most commonly prescribed. Among numerous trials of patients with PVD, aspirin as antiplatelet agent was associated with significant reduction in the risk of myocardial infarction and stroke^[32]. The combination of aspirin and dipyridamole (Persantine) was found to increase pain-free walking distance and resting limb blood flow^[33]. Clopidogrel (Plavix) was found to be more effective than aspirin in reducing combined risk of ischemic stroke, myocardial infarction or vascular death^[34]. Cilostazol (Pletal) is another antiplatelet agents and arterial vasodilator used for treatment of intermittent claudication. It is a phosphodiesterase inhibitor and a direct arterial vasodilator. This drug is approved by FDA for the treatment of intermittent claudication. It appears to be more effective than pentoxifylline^[35]. However, cilostazol has not been approved yet in Canada. Pentoxifylline (Trental) is a rheologic modifier used for the symptomatic relief of claudication. Studies investigating the efficacy of pentoxifylline have demonstrated conflicting results^[36]. A meta-analysis found that pentoxifylline improved walking distance by 29 meters compared with placebo. The improvement was 50% in placebo group, while pentoxifylline provided additional 30%. This benefit is substantially less than that achieved with a supervised exercise program^[31]. Ginkgo biloba is another product with antithrombic effect. It has been studied in patients with intermittent claudication with modest success^[37]. There are numerous studies which demonstrated that other modalities and therapies were not clinically beneficial in treating peripheral vascular disease. They include estrogen replacement therapy^[38], chelation therapy^[39], and vitamin E supplementation^[40]. There is also an extensive list of investigational agents with promising results. However, their clinical use is not yet recommended. Therapeutic angiogenesis is another therapeutic modality with a promising future. Animal studies have suggested that angiogenic growth factor can stimulate the development of collateral arteries^[41]. The safety and efficacy of therapeutic angiogenesis in humans is still under investigation^[42]. Immune modulation therapy is also a new therapeutic approach for treating intermittent claudication^[43] and involves the administration of autologous blood components following their *ex vivo* processing by exposure to thermal and oxidative stress. A relatively recent randomized, double blind, placebo - controlled study demonstrated that immune modulation therapy is a safe and effective treatment for patients with short distance claudication^[43].

PERCUTANEOUS INTERVENTIONAL PROCEDURES / SURGERY

Advancements in catheter, guide wire, and balloon design and development of intravascular stents have resulted in a dramatic increase in the number of percutaneous procedures performed. Much of this change in management has been the result of a published randomized trial showing no significant difference in outcome between successful percutaneous transluminal angioplasty and bypass surgery for PVD after a median follow-up period of four years^[44]. However, the long term success of percutaneous interventional procedures depends upon the site and length of lesion. Lesions which demonstrate unfavourable anatomy might be treated better surgically. Based upon natural history studies and quality of life measures, surgical revascularization procedures for intermittent claudication should be limited to low risk patients with disabling symptoms who can be expected to tolerate the procedure and live long enough to enjoy improved quality of life^[45]. The same criteria are used in diabetics even though they are at higher risk for a worse outcome^[45]. Patients who benefit most from surgical revascularization are generally under 70 years of age, non-diabetics and have little evidence of disease distal to the primary lesion^[45]. Regardless of whether surgery is performed, all patients with peripheral vascular disease should undergo evaluation and treatment of atherosclerotic risk factors. Risk factors modification prevents not only limb loss, but also myocardial infarction^[23]. Patients may also benefit from other areas of management, including supervised exercise and medications.

In conclusion, PVD is a prevalent and leading public health problem. It is associated with increased cardiovascular mortality and morbidity. Unfortunately, it is often under-diagnosed and under-treated. Ankle-brachial index is an inexpensive and reliable test for the screening of PVD. Aggressive control of risk factors, exercise rehabilitation and pharmacological interventions are highly effective in treatment of claudication and in reduction of cardiovascular events. At the end we should not forget primary care physicians, who are the first involved in screening, preventing and treating peripheral vascular disease. Updating their information is necessary to improve cardiovascular mortality and quality of life for a growing number of patients with PVD.

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